

# **BREYANZI- lisocabtagene maraleucel**

## **Juno Therapeutics, Inc.**

### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use BREYANZI safely and effectively. See full prescribing information for BREYANZI.

**BREYANZI® (lisocabtagene maraleucel) suspension for intravenous infusion**  
**Initial U.S. Approval: 2021**

#### **WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES**

*See full prescribing information for complete boxed warning.*

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving BREYANZI. Do not administer BREYANZI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids (2.2, 2.3, 5.1).**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving BREYANZI, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with BREYANZI. Provide supportive care and/or corticosteroids as needed (2.2, 2.3, 5.2).**
- **BREYANZI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BREYANZI REMS (5.3).**

#### **INDICATIONS AND USAGE**

BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B (1).

Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma (1, 14).

#### **DOSAGE AND ADMINISTRATION**

**For autologous use only. For intravenous use only.**

- Do NOT use a leukodepleting filter (2.2).
- Administer a lymphodepleting regimen of fludarabine and cyclophosphamide before infusion of BREYANZI (2.2).
- Verify the patient's identity prior to infusion (2.2).
- Premedicate with acetaminophen and an H<sub>1</sub> antihistamine (2.2).
- Confirm availability of tocilizumab prior to infusion (2.2, 5.1).
- Dosing of BREYANZI is based on the number of chimeric antigen receptor (CAR)-positive viable T cells (2.1).
- The dose is 50 to 110 × 10<sup>6</sup> CAR-positive viable T cells (consisting of CD8 and CD4 components) (2.1, 3).
- Administer BREYANZI in a certified healthcare facility (2.2, 5.1, 5.2, 5.3).

#### **DOSAGE FORMS AND STRENGTHS**

- BREYANZI is a cell suspension for infusion (3).
- A single dose of BREYANZI contains 50 to 110 × 10<sup>6</sup> CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied separately in one to four single-dose 5 mL vials (3). Each mL contains 1.5 × 10<sup>6</sup> to 70 × 10<sup>6</sup> CAR-positive viable T cells (3).

#### **CONTRAINDICATIONS**

None (4).

#### **WARNINGS AND PRECAUTIONS**

- **Hypersensitivity Reactions:** Monitor for hypersensitivity reactions during infusion (5.4).
- **Serious Infections:** Monitor patients for signs and symptoms of infection; treat appropriately (5.5).

- Prolonged Cytopenias: Patients may exhibit Grade 3 or higher cytopenias for several weeks following BREYANZI infusion. Monitor complete blood counts (5.6).
- Hypogammaglobulinemia: Monitor and consider immunoglobulin replacement therapy (5.7).
- Secondary Malignancies: In the event that a secondary malignancy occurs after treatment with BREYANZI, contact Bristol-Myers Squibb at 1-888-805-4555 (5.8).
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery for at least 8 weeks after BREYANZI administration (5.9).

#### ----- ADVERSE REACTIONS -----

The most common nonlaboratory adverse reactions (incidence greater than or equal to 20%) in BREYANZI-treated patients were fatigue, cytokine release syndrome, musculoskeletal pain, nausea, headache, encephalopathy, infections (pathogen unspecified), decreased appetite, diarrhea, hypotension, tachycardia, dizziness, cough, constipation, abdominal pain, vomiting, and edema (6.1).

**To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-888-805-4555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 2/2021**

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## **FULL PRESCRIBING INFORMATION**

### **WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES**

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving BREYANZI. Do not administer BREYANZI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids [see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.1)].**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving BREYANZI, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with BREYANZI. Provide supportive care and/or corticosteroids as needed [see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.2)].**
- **BREYANZI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BREYANZI REMS [see Warnings and Precautions (5.3)].**

## **1 INDICATIONS AND USAGE**

BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma [see Clinical Studies (14)].

## 2 DOSAGE AND ADMINISTRATION

**For autologous use only. For intravenous use only.**

### 2.1 Dose

A single dose of BREYANZI contains 50 to  $110 \times 10^6$  CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied separately in one to four single-dose vials.

See the respective Certificate of Release for Infusion (RFI Certificate) for each component, for the actual cell counts and volumes to be infused [*see Dosage and Administration (2.2) and Dosage Forms and Strengths (3)*].

### 2.2 Administration

BREYANZI is for autologous use only. The patient's identity must match the patient identifiers on the BREYANZI cartons, vials and syringe labels. Do not infuse BREYANZI if the information on the patient-specific labels does not match the intended patient.

#### Preparing the Patient for BREYANZI

Confirm the availability of BREYANZI before starting lymphodepleting chemotherapy.

#### *Pretreatment*

Administer the lymphodepleting chemotherapy regimen before infusion of BREYANZI: fludarabine 30 mg/m<sup>2</sup>/day intravenously (IV), and cyclophosphamide 300 mg/m<sup>2</sup>/day IV for 3 days. See the prescribing information for fludarabine and cyclophosphamide for information on dose adjustment in renal impairment.

Infuse BREYANZI 2 to 7 days after completion of lymphodepleting chemotherapy.

Delay the infusion of BREYANZI if the patient has unresolved serious adverse events from preceding chemotherapies, active uncontrolled infection, or active graft-versus-host disease (GVHD).

#### *Premedication*

To minimize the risk of infusion reactions, premedicate the patient with acetaminophen (650 mg orally) and diphenhydramine (25-50 mg, IV or orally), or another H1-antihistamine, 30 to 60 minutes prior to treatment with BREYANZI.

Avoid prophylactic use of systemic corticosteroids, as they may interfere with the activity of BREYANZI.

#### Receipt of BREYANZI

- BREYANZI is shipped directly to the cell-associated lab or clinical pharmacy associated with the infusion center in the vapor phase of a liquid nitrogen shipper.
- Confirm the patient's identity with the patient identifiers on the shipper.
- If the patient is not expected to be ready for administration before the shipper expires and the infusion site is qualified for onsite storage, transfer BREYANZI to onsite vapor phase of liquid nitrogen storage prior to preparation.
- If the patient is not expected to be ready for administration before the shipper expires and the infusion site is not qualified for onsite storage, contact Bristol-Myers Squibb at 1-888-805-4555 to arrange for return shipment.

## Preparing BREYANZI

### **Before thawing the vials**

- Confirm the patient's identity with the patient identifiers on the RFI Certificate.
- Read the RFI Certificate (affixed inside the shipper) for information on the number of syringes you will need to administer the CD8 and CD4 components (syringe labels are provided with the RFI Certificate). There is a separate RFI Certificate for each cell component.
- Confirm tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Confirm the infusion time in advance and adjust the start time of BREYANZI thaw such that it will be available for infusion when the patient is ready.

### *Thawing the vials*

1. Confirm the patient's identity with the patient identifiers on the outer carton and on the syringe labels.  
Once the vials of CAR-positive viable T cells (CD8 component and CD4 component) are removed from frozen storage, the thaw must be carried to completion and the cells administered within 2 hours.
2. Remove the CD8 component carton and CD4 component carton from the outer carton.
3. Confirm the patient's identity with the patient identifiers on the inner carton.
4. Open each inner carton and visually inspect the vial(s) for damage. If the vials are damaged, contact Bristol-Myers Squibb at 1-888-805-4555.
5. Confirm the patient's identity with the patient identifiers on the vials.
6. Carefully remove the vials from the cartons, place vials on a protective barrier pad, and thaw at room temperature until there is no visible ice in the vials. Thaw all of the vials at the same time.

**Keep the CD8 and CD4 components separate.**

### *Dose preparation*

- Prepare BREYANZI using sterile technique.
- Based on the concentration of CAR-positive viable T cells for each component, more than one vial of each of the CD8 and CD4 components may be required to complete a dose. A separate syringe should be prepared for each CD8 or CD4 component vial received.

**Note:** The volume to be drawn up and infused may differ for each component as indicated on the RFI Certificate. Do NOT draw up excess volume into the syringe.

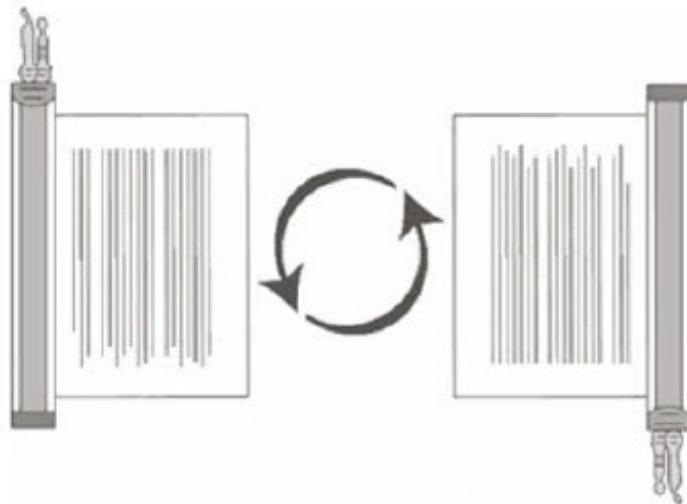
- Each vial contains 5 mL with a total extractable volume of 4.6 mL of CD8 or CD4 component T cells. The RFI Certificate for each component indicates the volume (mL) of cells to be drawn up into each syringe. Use the smallest Luer-lock tip syringe necessary (1, 3, or 5 mL) to draw up the specified volume from each vial. A 5 mL syringe should not be used for volumes less than 3 mL.

7. **Prepare the syringe(s) of the CD8 component first.** Affix the CD8 syringe labels to the syringe(s) prior to pulling the required volume into the syringe(s).

**Note:** It is important to confirm that the volume drawn up for each component matches the volume specified in the respective RFI Certificate. Do NOT draw up excess volume into the syringe.

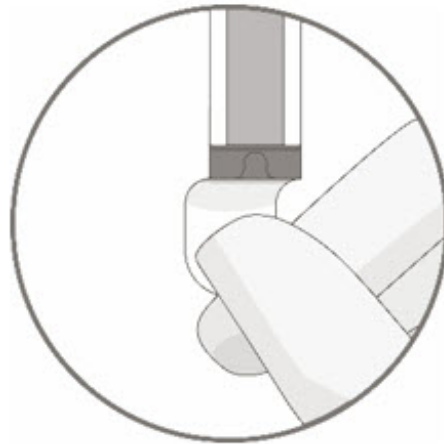
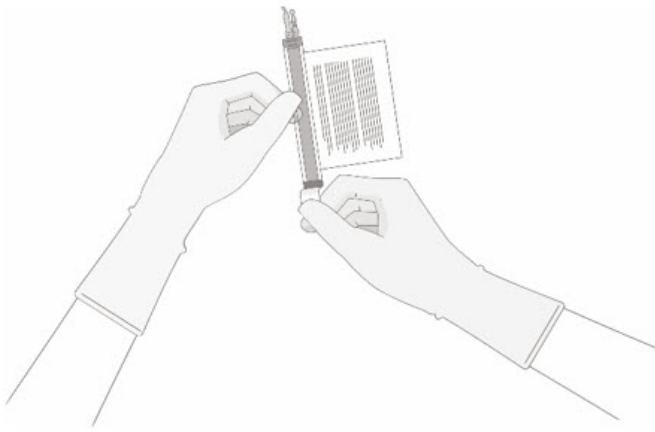
Withdrawal of the required volume of cells from each vial into a separate syringe should be carried out using the following instructions:

8. Hold the thawed vial(s) upright and gently invert the vial(s) 5 times to mix the cell product. If any clumping is apparent, continue to invert the vial(s) until clumps have dispersed and cells appear to be evenly resuspended.



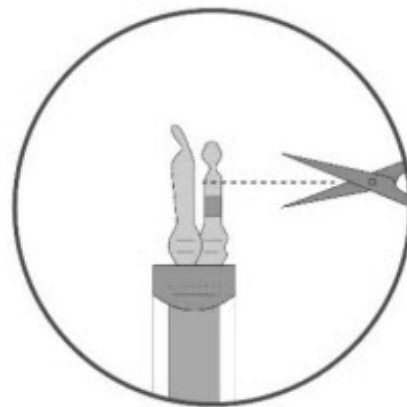
Vial upright → Vial inverted

9. Visually inspect the thawed vial(s) for damage or leaks. Do not use if the vial is damaged or if the clumps do not disperse; contact Bristol-Myers Squibb at 1-888-805-4555. The liquid in the vials should be slightly opaque to opaque, colorless to yellow or brownish-yellow.
10. Remove the polyaluminum cover (if present) from the bottom of the vial and swab the septum with an alcohol wipe. Allow to air dry before proceeding.  
**NOTE:** The absence of the polyaluminum cover does not impact the sterility of the vial.



11. Keeping the vial(s) upright, cut the seal on the tubing line on the top of the vial immediately above the filter to open the air vent on the vial.

**NOTE:** Be careful to select the correct tubing line with the filter. Cut ONLY the tubing with a filter.

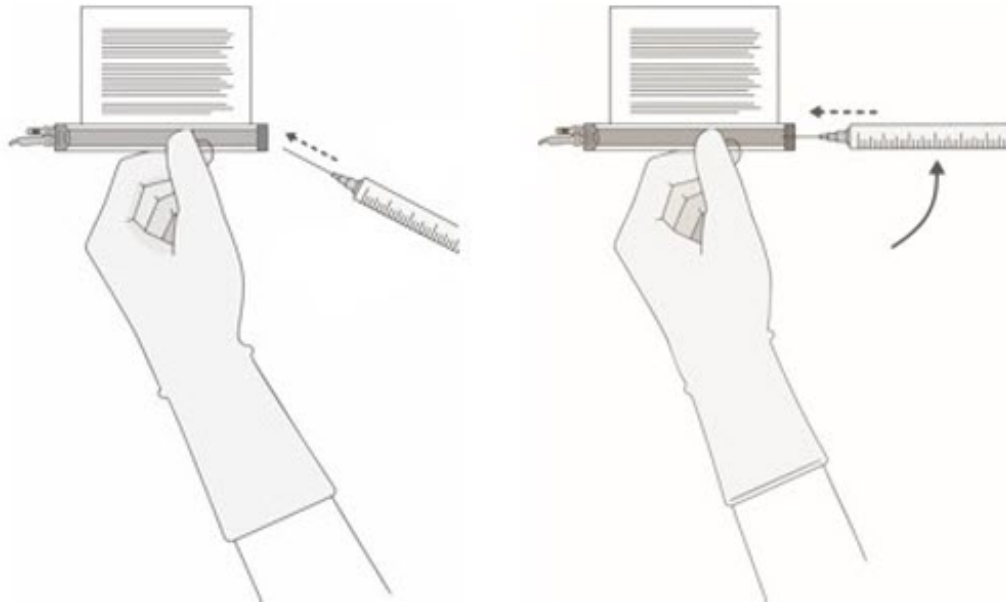


12. Hold a 20-gauge, 1-1 ½ inch needle, with the opening of the needle tip away from the retrieval port septum.

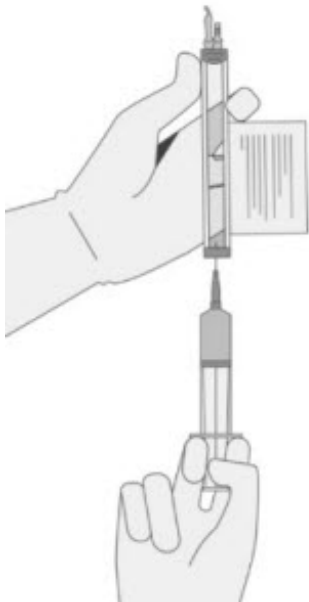
- Insert the needle into the septum at a 45°- 60° angle to puncture the retrieval port septum.
- Increase the angle of the needle gradually as the needle enters the vial.

a

b

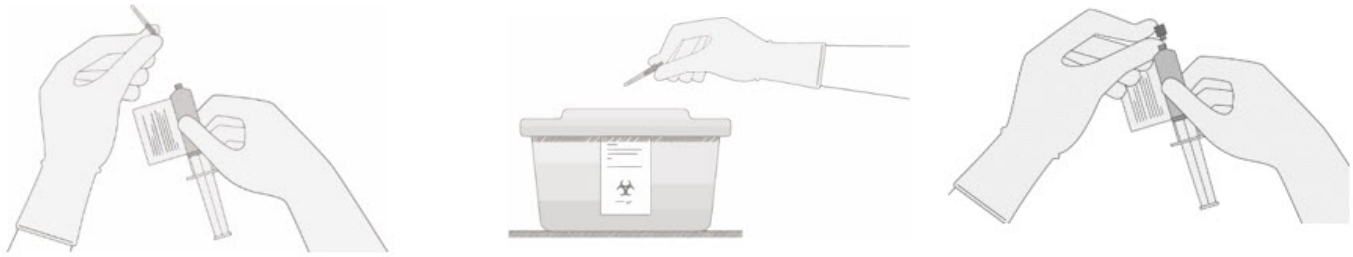


13. WITHOUT drawing air into the syringe, slowly withdraw the target volume (as specified in the RFI Certificate). Carefully inspect the syringe for signs of debris prior to proceeding. If there is debris, contact Bristol-Myers Squibb at 1-888-805-4555.



14. Verify that the volume of CD8/CD4 component matches the volume specified for the relevant component in the RFI Certificate. Once the volume is verified, remove the syringe/needle from the vial, carefully detach the needle from the syringe and cap the syringe.





15. Continue to keep the vial horizontal and return it to the carton to avoid leaking from the vial.
16. Dispose of any unused portion of BREYANZI (according to local biosafety guidelines).
17. Repeat the process steps 7-16 for the CD4 Component.
18. Transport the labeled CD8 and CD4 syringes to the bedside by placing with protective barrier pad inside an insulated room temperature container.

#### BREYANZI Administration

- **Do NOT** use a leukodepleting filter.
  - Ensure tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
  - Confirm the patient's identity matches the patient identifiers on the syringe label.
  - Once BREYANZI has been drawn into syringes, proceed with administration as soon as possible. The total time from removal from frozen storage to patient administration should not exceed 2 hours as indicated by the time entered on the syringe label.
1. Use intravenous normal saline to flush all the infusion tubing prior to and after each CD8 or CD4 component administration.
  2. Administer the entire volume of the CD8 component intravenously at an infusion rate of approximately 0.5 mL/minute, using the closest port or Y-arm.  
**NOTE:** The time for infusion will vary but will usually be less than 15 minutes for each component.
  3. If more than one syringe is required for a full cell dose of the CD8 component, administer the volume in each syringe consecutively without any time between administering the contents of the syringes (unless there is a clinical reason (e.g., infusion reaction) to hold the dose).
  4. After the CD8 component has been administered, flush the tubing with normal saline, using enough volume to clear the tubing and the length of the IV catheter.
  5. Administer the CD4 component second, immediately after administration of the CD8 component is complete, using steps 1-4, as described for the CD8 component. Following administration of the CD4 component, flush the tubing with normal saline, using enough volume to clear the tubing and the length of the IV catheter.

BREYANZI contains human blood cells that are genetically modified with replication-incompetent, self-inactivating lentiviral vector. Follow universal precautions and local biosafety guidelines applicable for the handling and disposal, to avoid potential transmission of infectious diseases.

## Monitoring

- Administer BREYANZI at a REMS-certified healthcare facility.
- Monitor patients daily at a certified healthcare facility during the first week following infusion for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.
- Refrain from driving or hazardous activities for 8 weeks.

## **2.3 Management of Severe Adverse Reactions**

### Cytokine Release Syndrome

Identify cytokine release syndrome (CRS) based on clinical presentation [see *Warnings and Precautions* (5.1)]. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

If concurrent neurologic toxicity is suspected during CRS, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to the CRS grade in Table 1
- Antiseizure medication according to the neurologic toxicity in Table 2

**Table 1: CRS Grading and Management Guidance**

<b>CRS Grade*</b>	<b>Tocilizumab</b>	<b>Corticosteroids†</b>
<b>Grade 1</b> Fever	If less than 72 hours after infusion, consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). If 72 hours or more after infusion, treat symptomatically.	If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 24 hours. If 72 hours or more after infusion, treat symptomatically.
<b>Grade 2</b> Symptoms require and respond to moderate intervention. Oxygen requirement less	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour	If less than 72 hours after infusion, administer dexamethasone 10 mg IV every 12-24 hours. If 72 hours or more after infusion, consider dexamethasone 10 mg IV every 12-24 hours.

than 40% FiO <sub>2</sub> , or hypotension responsive to fluids or low dose of one vasopressor, or Grade 2 organ toxicity.	period; maximum total of 4 doses.	
	<p>If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (10-20 mg IV every 6 to 12 hours).</p> <p>If no improvement or continued rapid progression, maximize dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.</p>	
<b>Grade 3</b>	Per Grade 2.	Administer dexamethasone 10 mg IV every 12 hours.
Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO <sub>2</sub> , or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity, or Grade 4 transaminitis.	<p>If no improvement within 24 hours or rapid progression of CRS, repeat tocilizumab and escalate dose and frequency of dexamethasone (10-20 mg IV every 6 to 12 hours).</p> <p>If no improvement or continued rapid progression, maximize dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.</p>	
<b>Grade 4</b>	Per Grade 2.	Administer dexamethasone 20 mg IV every 6 hours.
Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	<p>If no improvement within 24 hours or rapid progression of CRS, escalate tocilizumab and corticosteroid use. If no improvement or continued rapid progression, maximize dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.</p>	

\* Lee criteria for grading CRS (Lee et al, 2014).

† If corticosteroids are initiated, continue corticosteroids for at least 3 doses or until complete resolution of symptoms, and consider corticosteroid taper.

## Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. If neurologic toxicity is suspected, manage according to the recommendations in Table 2.

If concurrent CRS is suspected during neurologic toxicity, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to the CRS grade in Table 1
- Antiseizure medication according to the neurologic toxicity in Table 2

**Table 2: Neurologic Toxicity (NT) Grading and Management Guidance**

<b>NT Grade*</b>	<b>Corticosteroids and Antiseizure Medication</b>
<b>Grade 1</b>	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.
<b>Grade 2</b>	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 mg IV every 12 hours for 2-3 days, or longer for persistent symptoms. Consider taper for a total steroid exposure of greater than 3 days. If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to a maximum of 20 mg IV every 6 hours. If no improvement after another 24 hours, rapidly progressing symptoms, or life-threatening complications arise, give methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided 4 times a day; taper within 7 days).
<b>Grade 3</b>	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 to 20 mg IV every 8 to 12 hours. Steroids are not recommended for isolated Grade 3 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (dose and frequency as per Grade 2). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 g/m <sup>2</sup> .
<b>Grade 4</b>	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (dose and frequency as per Grade 2).

If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m<sup>2</sup>.

\* NCI CTCAE criteria for grading neurologic toxicities version. 4.03.

### 3 DOSAGE FORMS AND STRENGTHS

BREYANZI is a cell suspension for infusion.

A single dose of BREYANZI contains of 50 to 110 × 10<sup>6</sup> CAR-positive viable T cells, consisting of CD8 and CD4 components, with each component supplied separately in single-dose vials.

More than one vial of each of the CD8 component and/or CD4 component may be needed to achieve the dose of BREYANZI.

Each vial contains between 6.9 × 10<sup>6</sup> and 322 × 10<sup>6</sup> CAR-positive viable T cells in 4.6 mL cell suspension (between 1.5 × 10<sup>6</sup> and 70 × 10<sup>6</sup> CAR-positive viable T cells/mL).

The infusion volume is calculated based on the concentration of cryopreserved drug product CAR-positive viable T cells concentration. The volume may differ for each component infused. See the RFI Certificate for details [see *How Supplied/Storage and Handling (16)*].

### 4 CONTRAINDICATIONS

None.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Cytokine Release Syndrome

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with BREYANZI. CRS occurred in 46% (122/268) of patients receiving BREYANZI, including ≥ Grade 3 (Lee grading system<sup>1</sup>) CRS in 4% (11/268) of patients. One patient had fatal CRS and 2 had ongoing CRS at time of death. The median time to onset was 5 days (range: 1 to 15 days). CRS resolved in 119 of 122 patients (98%) with a median duration of 5 days (range: 1 to 17 days). Median duration of CRS was 5 days (range 1 to 30 days) in all patients, including those who died or had CRS ongoing at time of death.

Among patients with CRS, the most common manifestations of CRS include fever (93%), hypotension (49%), tachycardia (39%), chills (28%), and hypoxia (21%) [see *Adverse Reactions (6.1)*]. Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, diffuse alveolar damage, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) [see *Adverse Reactions (6.1)*].

Ensure that 2 doses of tocilizumab are available prior to infusion of BREYANZI.

Sixty-one of 268 (23%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of BREYANZI. Twenty-seven (10%) patients received tocilizumab only, 25 (9%) received tocilizumab and a corticosteroid, and 9 (3%) received corticosteroids only.

Monitor patients daily at a certified healthcare facility during the first week following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time [see *Patient Counseling Information* (17)]. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated [see *Dosage and Administration* (2.3)].

## 5.2 Neurologic Toxicities

Neurologic toxicities that were fatal or life-threatening, occurred following treatment with BREYANZI. CAR T cell-associated neurologic toxicities occurred in 35% (95/268) of patients receiving BREYANZI, including  $\geq$  Grade 3 in 12% (31/268) of patients. Three patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at time of death. The median time to onset of the first event was 8 days (range: 1 to 46 days). The onset of all neurologic events occurred within the first 8 weeks following BREYANZI infusion. Neurologic toxicities resolved in 81 of 95 patients (85%) with a median duration of 12 days (range: 1 to 87 days). Three of four patients with ongoing neurologic toxicity at data cutoff had tremor and one subject had encephalopathy. Median duration of neurologic toxicity was 15 days (range: 1 to 785 days) in all patients, including those with ongoing neurologic events at the time of death or at data cutoff.

Seventy-eight (78) of 95 (82%) patients with neurologic toxicity experienced CRS. Neurologic toxicity overlapped with CRS in 57 patients. The onset of neurologic toxicity was after onset of CRS in 30 patients, before CRS onset in 13 patients, same day as CRS onset in 7 patients, and same day as CRS resolution in 7 patients. Neurologic toxicity resolved in three patients before the onset of CRS. Eighteen patients experienced neurologic toxicity after resolution of CRS.

The most common neurologic toxicities included encephalopathy (24%), tremor (14%), aphasia (9%), delirium (7%), headache (7%), ataxia (6%), and dizziness (6%). Serious events including cerebral edema and seizures occurred with BREYANZI. Fatal and serious cases of leukoencephalopathy, some attributable to fludarabine, have occurred in patients treated with BREYANZI.

Monitor patients daily at a certified healthcare facility during the first week following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for at least 4 weeks after infusion; evaluate and treat promptly [see *Dosage and Administration* (2.3)]. Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time [see *Patient Counseling Information* (17)].

## 5.3 BREYANZI REMS

Because of the risk of CRS and neurologic toxicities, BREYANZI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BREYANZI REMS [see *Boxed Warning and Warnings and Precautions* (5.1, 5.2)]. The required components of the BREYANZI REMS are:

- Healthcare facilities that dispense and administer BREYANZI must be enrolled and comply with the REMS requirements.
- Certified healthcare facilities must have on-site, immediate access to tocilizumab.
- Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after BREYANZI infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer BREYANZI are trained on the management of CRS and neurologic toxicities.

Further information is available at [www.BreyanziREMS.com](http://www.BreyanziREMS.com), or contact Bristol-Myers Squibb at 1-888-423-5436.

## **5.4 Hypersensitivity Reactions**

Allergic reactions may occur with the infusion of BREYANZI. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO).

## **5.5 Serious Infections**

Severe infections, including life-threatening or fatal infections, have occurred in patients after BREYANZI infusion. Infections (all grades) occurred in 45% (121/268) of patients. Grade 3 or higher infections occurred in 19% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections occurred in 5%, and viral and fungal infections occurred in 1.5% and 0.4% of patients, respectively. Monitor patients for signs and symptoms of infection before and after BREYANZI administration and treat appropriately. Administer prophylactic antimicrobials according to standard institutional guidelines.

Febrile neutropenia has been observed in 9% (24/268) of patients after BREYANZI infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.

Avoid administration of BREYANZI in patients with clinically significant active systemic infections.

### Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells.

Ten of the 11 patients in the TRANSCEND study with a prior history of HBV were treated with concurrent antiviral suppressive therapy to prevent HBV reactivation during and after treatment with BREYANZI.

Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

## **5.6 Prolonged Cytopenias**

Patients may exhibit cytopenias not resolved for several weeks following lymphodepleting chemotherapy and BREYANZI infusion.

Grade 3 or higher cytopenias persisted at Day 29 following BREYANZI infusion in 31%

(84/268) of patients, and included thrombocytopenia (26%), neutropenia (14%), and anemia (3.0%). Monitor complete blood counts prior to and after BREYANZI administration.

## **5.7 Hypogammaglobulinemia**

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with BREYANZI. The adverse event of hypogammaglobulinemia was reported as an adverse reaction in 14% (37/268) of patients; laboratory IgG levels fell below 500 mg/dL after infusion in 21% (56/268) of patients. Hypogammaglobulinemia, either as an adverse reaction or laboratory IgG level below 500 mg/dL after infusion, was reported in 32% (85/268) of patients.

Monitor immunoglobulin levels after treatment with BREYANZI and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement as clinically indicated.

### Live Vaccines

The safety of immunization with live viral vaccines during or following BREYANZI treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during BREYANZI treatment, and until immune recovery following treatment with BREYANZI.

## **5.8 Secondary Malignancies**

Patients treated with BREYANZI may develop secondary malignancies. Monitor lifelong for secondary malignancies. In the event that a secondary malignancy occurs, contact Bristol-Myers Squibb at 1-888-805-4555 for reporting and to obtain instructions on collection of patient samples for testing.

## **5.9 Effects on Ability to Drive and Use Machines**

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving BREYANZI are at risk for altered or decreased consciousness or impaired coordination in the 8 weeks following BREYANZI administration. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

## **6 ADVERSE REACTIONS**

The following adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1, 5.3)]*
- Neurologic Toxicities *[see Warnings and Precautions (5.2, 5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*
- Serious Infections *[see Warnings and Precautions (5.5)]*
- Prolonged Cytopenias *[see Warnings and Precautions (5.6)]*
- Hypogammaglobulinemia *[see Warnings and Precautions (5.7)]*

## **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction



rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to BREYANZI in the TRANSCEND study, in which 268 adult patients with R/R large B-cell lymphoma received a flat dose of CAR-positive viable T cells [see *Clinical Studies (14)*]. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow-up was 9 months. The median age of the study population was 63 years (range: 18 to 86 years); 65% were male. The Eastern Cooperative Oncology Group (ECOG) performance status at screening was 0 in 41% of patients, 1 in 58% of patients, and 2 in 1.5% of patients.

Serious adverse reactions occurred in 46% of patients. The most common nonlaboratory, serious adverse reactions (> 2%) were CRS, encephalopathy, sepsis, febrile neutropenia, aphasia, pneumonia, fever, hypotension, dizziness, and delirium. Fatal adverse reactions occurred in 4% of patients.

Table 3 presents the adverse reactions reported in at least 10% of patients treated with BREYANZI, and Table 4 describes the laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients.

The most common nonlaboratory adverse reactions of any grade ( $\geq 20\%$ ) were fatigue, CRS, musculoskeletal pain, nausea, headache, encephalopathy, infections (pathogen unspecified), decreased appetite, diarrhea, hypotension, tachycardia, dizziness, cough, constipation, abdominal pain, vomiting, and edema.

**Table 3: Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with BREYANZI in the TRANSCEND Study (N=268)**

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
<b>Cardiac disorders</b>		
Tachycardia <sup>a</sup>	25	0
<b>Gastrointestinal disorders</b>		
Nausea	33	1.5
Diarrhea	26	0.4
Constipation	23	0
Abdominal pain <sup>b</sup>	21	3.0
Vomiting	21	0.4
<b>General disorders and administration site conditions</b>		
Fatigue <sup>c</sup>	48	3.4
Edema <sup>d</sup>	21	1.1
Fever	16	0
Chills	12	0
<b>Immune system disorders</b>		
Cytokine release syndrome	46	4.1
Hypogammaglobulinemia <sup>e</sup>	32	0

<b>Infections and infestations<sup>f</sup></b>		
Infections - pathogen unspecified <sup>g</sup>	29	16
Bacterial infectious disorders <sup>h</sup>	13	5
Upper respiratory tract infection <sup>i</sup>	13	0.7
Viral infectious disorders	10	1.5
<b>Metabolism and nutrition disorders</b>		
Decreased appetite	28	2.6
<b>Musculoskeletal and connective tissue disorders</b>		
Musculoskeletal pain <sup>j</sup>	37	2.2
Motor dysfunction <sup>k</sup>	10	1.1
<b>Nervous system disorders</b>		
Headache <sup>l</sup>	30	1.1
Encephalopathy <sup>m</sup>	29	9
Dizziness <sup>n</sup>	24	2.6
Tremor <sup>o</sup>	16	0
Peripheral neuropathy <sup>p</sup>	11	0
Aphasia <sup>q</sup>	10	2.2
<b>Psychiatric disorders</b>		
Insomnia <sup>r</sup>	14	0.4
Anxiety <sup>s</sup>	10	0
Delirium <sup>t</sup>	10	2.2
<b>Renal and urinary disorders</b>		
Renal failure <sup>u</sup>	11	3.0
<b>Respiratory, thoracic, and mediastinal disorders</b>		
Cough <sup>v</sup>	23	0
Dyspnea <sup>w</sup>	16	2.6
<b>Skin and subcutaneous tissue disorders</b>		
Rash <sup>x</sup>	13	0.4
<b>Vascular disorders</b>		
Hypotension <sup>y</sup>	26	3.4
Hypertension	14	4.5
Hemorrhage <sup>z</sup>	10	1.5

<sup>a</sup> Tachycardia includes heart rate increased, sinus tachycardia, tachycardia.

<sup>b</sup> Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.

<sup>c</sup> Fatigue includes asthenia, fatigue, malaise.

<sup>d</sup> Edema includes edema, edema peripheral, fluid overload, fluid retention, generalized edema, hypervolemia, peripheral swelling, pulmonary congestion, pulmonary edema, swelling.

<sup>e</sup> Hypogammaglobulinemia includes subjects with adverse events of hypogammaglobulinemia (14%) and/or laboratory IgG levels

that fell below 500 mg/dL after infusion (21%).

<sup>f</sup> Infections and infestations are grouped by pathogen type and selected clinical syndromes.

<sup>g</sup> Infections – pathogen unspecified contains febrile neutropenia (9%).

<sup>h</sup> Bacterial infection includes infections by pathogen type plus appendicitis, diverticulitis, peritonitis, skin infection, tooth infection.

<sup>i</sup> Upper respiratory tract infections include nasopharyngitis, pharyngitis, rhinitis, rhinovirus infection, sinusitis, upper respiratory tract congestion, upper respiratory tract infection.

<sup>j</sup> Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, pain in extremity, spinal pain.

<sup>k</sup> Motor dysfunction includes eyelid ptosis, motor dysfunction, muscle rigidity, muscle spasms, muscle spasticity, muscle tightness, muscle twitching, muscular weakness, myoclonus, myopathy.

<sup>l</sup> Headache includes headache, head discomfort, migraine, sinus headache.

<sup>m</sup> Encephalopathy includes amnesia, bradyphrenia, cognitive disorder, confusional state, depersonalization/derealization disorder, depressed level of consciousness, disturbance in attention, encephalopathy, flat affect, hypersomnia, incoherent, lethargy, leukoencephalopathy, loss of consciousness, memory impairment, mental impairment, mental status changes, somnolence.

<sup>n</sup> Dizziness includes dizziness, presyncope, syncope, vertigo.

<sup>o</sup> Tremor includes essential tremor, resting tremor, tremor.

<sup>p</sup> Peripheral neuropathy includes hyperesthesia, hypoesthesia, meralgia paresthetica, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, sciatica, sensory loss.

<sup>q</sup> Aphasia includes aphasia, disorganized speech, dysarthria, dysphemia, dysphonia, slow speech, speech disorder.

<sup>r</sup> Insomnia includes insomnia, somnambulism.

<sup>s</sup> Anxiety includes anxiety, panic attack.

<sup>t</sup> Delirium includes agitation, delirium, delusion, disorientation, hallucination, 'hallucination, visual', irritability, restlessness.

<sup>u</sup> Renal failure includes acute kidney injury, blood creatinine increased, chronic kidney disease, renal failure, renal injury.

<sup>v</sup> Cough includes cough, productive cough, upper-airway cough syndrome.

<sup>w</sup> Dyspnea includes acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure.

<sup>x</sup> Rash includes erythema, dermatitis acneiform, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular,

rash morbilliform, rash papular, rash pruritic, rash pustular.

<sup>Y</sup> Hypotension includes hypotension, orthostatic hypotension.

<sup>Z</sup> Hemorrhage includes catheter site hemorrhage, conjunctival hemorrhage, epistaxis, hematoma, hematuria, hemorrhage, hemorrhage intracranial, pulmonary hemorrhage, retinal hemorrhage, vaginal hemorrhage.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with BREYANZI include the following:

- *Blood and lymphatic system disorders*: Coagulopathy (1.5%)
- *Cardiac disorders*: Arrhythmia (6%), cardiomyopathy (1.5%)
- *Gastrointestinal disorders*: Gastrointestinal hemorrhage (4.1%)
- *Infections and infestations*: Pneumonia (8%), fungal infections (8%), sepsis (4.5%), urinary tract infection (4.1%)
- *Injury, poisoning, and procedural complications*: Infusion-related reaction (1.9%)
- *Metabolism and nutrition disorders*: Tumor lysis syndrome (0.7%)
- *Nervous system disorders*: Ataxia/gait disturbance (7%), visual disturbance (5%), paresis (2.6%), cerebrovascular events (1.9%), seizure (1.1%), brain edema (0.4%)
- *Respiratory, thoracic, and mediastinal disorders*: Pleural effusion (7%), hypoxia (6%)
- *Vascular disorder*: Thrombosis (7%)

**Table 4: Grade 3 or 4 Treatment Emergent Laboratory Abnormalities Occurring in  $\geq$  10% of Patients Following Treatment with BREYANZI in the TRANSCEND Study\* (N=268)**

Laboratory Abnormality	Grade 3 or 4 (%)
Neutropenia	76
Thrombocytopenia	39
Anemia	23
Hypofibrinogenemia	15
Hypophosphatemia	13

\* NCI CTCAE=Common Terminology Criteria for Adverse Events version 4.03.

## 6.2 Immunogenicity

BREYANZI has the potential to induce anti-product antibodies. The immunogenicity of BREYANZI has been evaluated using an electrochemiluminescence (ECL) immunoassay for the detection of binding antibodies against the extracellular CD19-binding domain of BREYANZI. Pre-existing anti-product antibodies were detected in 11% (28/261) of patients. Treatment-induced or treatment-boosted anti-product antibodies were detected in 11% (27/257) of patients. Due to the small number of patients who had anti-product antibodies, the relationship between anti-product antibody status and efficacy, safety, or pharmacokinetics was not conclusive.

## 7 DRUG INTERACTIONS

## **7.1 Drug-laboratory Test Interactions**

HIV and the lentivirus used to make BREYANZI have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received BREYANZI.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

There are no available data with BREYANZI use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with BREYANZI to assess whether it can cause fetal harm when administered to a pregnant woman.

It is not known if BREYANZI has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia and hypogammaglobulinemia. Therefore, BREYANZI is not recommended for women who are pregnant, and pregnancy after BREYANZI infusion should be discussed with the treating physician.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

### **8.2 Lactation**

#### Risk Summary

There is no information regarding the presence of BREYANZI in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BREYANZI and any potential adverse effects on the breastfed infant from BREYANZI or from the underlying maternal condition.

### **8.3 Females and Males of Reproductive Potential**

#### Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually active females of reproductive potential should have a pregnancy test prior to starting treatment with BREYANZI.

#### Contraception

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with BREYANZI.

#### Infertility

There are no data on the effects of BREYANZI on fertility.

## 8.4 Pediatric Use

The safety and efficacy of BREYANZI have not been established in pediatric patients.

## 8.5 Geriatric Use

In clinical trials of BREYANZI, 111 (41%) of the 268 patients in TRANSCEND were 65 years of age or older, and 27 (10%) were 75 years of age or older. No clinically important differences in safety or effectiveness of BREYANZI were observed between these patients and younger patients.

## 11 DESCRIPTION

BREYANZI (lisocabtagene maraleucel) is a CD19-directed genetically modified autologous T cell immunotherapy administered as a defined composition of CAR-positive viable T cells (consisting of CD8 and CD4 components). The CAR is comprised of the FMC63 monoclonal antibody-derived single-chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. In addition, BREYANZI includes a nonfunctional truncated epidermal growth factor receptor (EGFRt) that is co-expressed on the cell surface with the CD19-specific CAR.

BREYANZI is a T-cell product. BREYANZI is prepared from the patient's T cells, which are obtained from the product of a standard leukapheresis procedure. The purified CD8-positive and CD4-positive T cells are separately activated and transduced with the replication-incompetent lentiviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved as separate CD8 and CD4 component vials that together constitute a single dose of BREYANZI. The product must pass a sterility test before release for shipping as a frozen suspension in patient-specific vials. The product is thawed prior to administration [see *Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)*].

The BREYANZI formulation contains 75% (v/v) Cryostor® CS10 [containing 7.5% dimethylsulfoxide (v/v)], 24% (v/v) Multiple Electrolytes for Injection, Type 1, 1% (v/v) of 25% albumin (human).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

BREYANZI is a CD19-directed genetically modified autologous cell immunotherapy administered as a defined composition to reduce variability in CD8-positive and CD4-positive T cell dose. The CAR is comprised of an FMC63 monoclonal antibody-derived single chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. CD3 zeta signaling is critical for initiating activation and antitumor activity, while 4-1BB (CD137) signaling enhances the expansion T cell and persistence of BREYANZI.

CAR binding to CD19 expressed on the cell surface of tumor and normal B cells induces activation and proliferation of CAR T cells, release of pro-inflammatory cytokines, and

cytotoxic killing of target cells.

## 12.2 Pharmacodynamics

Following BREYANZI infusion, pharmacodynamic responses were evaluated over a 4-week period by measuring transient elevation of soluble biomarkers such as cytokines, chemokines, and other molecules. Peak elevation of soluble biomarkers was observed within the first 14 days after BREYANZI infusion and returned to baseline levels within 28 days.

B-cell aplasia, defined as CD19+ B cells comprising less than 3% of peripheral blood lymphocytes, is an on-target effect of BREYANZI. B-cell aplasia was observed in the majority of patients for up to 1 year following BREYANZI infusion.

## 12.3 Pharmacokinetics

Following infusion, BREYANZI exhibited an initial expansion followed by a bi-exponential decline. The median time of maximal expansion in peripheral blood occurred 12 days after the first infusion. BREYANZI was present in peripheral blood for up to 2 years.

Responders (N=135) had a 2.28-fold higher median  $C_{max}$  than nonresponders (N=37) (35,335 vs. 15,527 copies/ $\mu$ g). Responders had a 1.76-fold higher median  $AUC_{0-28d}$  than nonresponders (273,552 vs. 155,240 day\*copies/ $\mu$ g).

Some patients required tocilizumab and corticosteroids for the management of CRS and neurologic toxicities. Patients treated with tocilizumab (N=49) had a 3.63-fold and 3.69-fold higher median  $C_{max}$  and  $AUC_{0-28d}$ , respectively, compared to patients who did not receive tocilizumab (N=189). Similarly, patients who received corticosteroids (N=50) had a 3.76-fold and 3.69-fold higher median  $C_{max}$  and  $AUC_{0-28d}$ , respectively, compared to patients who did not receive corticosteroids (N=188).

Patients < 65 years old (N=142) had a 3.06-fold and 2.30-fold higher median  $C_{max}$  and  $AUC_{0-28d}$ , respectively, compared to patients  $\geq$  65 years old (N=96). Sex, race, ethnicity, and body weight did not show clear relationships to  $C_{max}$  and  $AUC_{0-28d}$ .

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with BREYANZI. No studies have been conducted to evaluate the effects of BREYANZI on fertility. *In vitro* studies with BREYANZI manufactured from healthy donors and patients showed no evidence for transformation and/or immortalization and no preferential integration near genes associated with oncogenic transformation.

## 14 CLINICAL STUDIES

### Relapsed or Refractory Large B-Cell Lymphoma

The efficacy of BREYANZI was evaluated in an open-label, multicenter, single-arm trial (TRANSCEND; NCT02631044) in adult patients with relapsed or refractory large B-cell non-Hodgkin lymphoma after at least 2 lines of therapy. The study included patients with ECOG performance status  $\leq$  2, prior autologous and/or allogeneic hematopoietic stem

cell transplant (HSCT), and secondary CNS lymphoma involvement. The study excluded patients with a creatinine clearance of less than 30 mL/min, alanine aminotransferase > 5 times the upper limit of normal, or left ventricular ejection fraction < 40%. There was no prespecified threshold for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy. Bridging therapy for disease control was permitted between apheresis and the start of lymphodepleting chemotherapy, including intrathecal chemotherapy or radiation therapy for treatment of CNS involvement with lymphoma.

BREYANZI was administered two to seven days following completion of lymphodepleting chemotherapy. The lymphodepleting chemotherapy regimen consisted of fludarabine 30 mg/m<sup>2</sup>/day and cyclophosphamide 300 mg/m<sup>2</sup>/day concurrently for 3 days. BREYANZI was administered in the inpatient and outpatient setting.

Of 299 patients who underwent leukapheresis for whom BREYANZI was manufactured in the dose range of 50 to 110 × 10<sup>6</sup> CAR-positive viable T cells:

- 44 (15%) did not receive CAR-positive T cells either due to manufacturing failures (n=2), death (n=29), disease complications (n=6), or other reasons (n=7)
- 204 (68%) received BREYANZI in the intended dose range, of whom 192 were evaluable for efficacy (main efficacy population); 12 were not evaluable due to absence of PET positive disease at study baseline or after bridging therapy
- 51 (17%) either received BREYANZI outside of the intended dose range (n=26) or received CAR-positive T cells that did not meet the product specifications for BREYANZI (manufacturing failures; n=25).

Of the 192 patients in the main efficacy population, the median age was 63 years (range: 18 to 86 years), 69% were male, 84% were white, 6% were black, and 4.7% were Asian. The median number of prior therapies was 3 (range: 1 to 8). Diagnoses were de novo DLBCL (53%), DLBCL transformed from indolent lymphoma (25%), high-grade B-cell lymphoma (14%), primary mediastinal large B-cell lymphoma (7%), follicular lymphoma, grade 3B (1.0%). Of these patients, 64% had disease refractory to last therapy, 53% had primary refractory disease, 37% had prior HSCT and 2.6% had CNS involvement.

Efficacy was based on complete response (CR) rate and duration of response (DOR), as determined by an independent review committee (IRC) using 2014 Lugano criteria (Tables 5 and 6). The median time to first response (CR or partial response [PR]) was 1.0 month (range: 0.7 to 8.9 months). The median time to first CR was 1.0 month (range 0.8 to 12.5 months). Of the 104 patients who achieved CR, 23 initially had stable disease (6 patients) or PR (17 patients), with a median time to improvement of 2.2 months (range: 0.7 to 11.6 months).

**Table 5: Response Rate in Main Efficacy Population**

	<b>BREYANZI-treated N=192</b>
<b>Overall Response Rate*, n</b> [95% CI]	141 (73%) [67%, 80%]
<b>Complete Response, n</b> [95% CI]	104 (54%) [47%, 61%]
<b>Partial Response, n</b>	37 (19%)



[95% CI]	[14%, 26%]
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CI=confidence interval.

\* Per the Lugano criteria, as assessed by an IRC.

**Table 6: Duration of Response**

	<b>BREYANZI-treated*</b> <b>N=192</b>
<b>Number of Responders</b>	<b>141</b>
<b>DOR (Months)</b>	
Median	16.7
[95% CI] <sup>†</sup>	[5.3, NR]
Range <sup>‡</sup>	0.0+ to 23.5+
<b>DOR if Best Response is CR (Months)</b>	
Median	NR
[95% CI] <sup>†</sup>	[16.7, NR]
Range <sup>‡</sup>	0.7+ to 23.5+
<b>DOR if Best Response is PR (Months)</b>	
Median	1.4
[95% CI] <sup>†</sup>	[1.1, 2.2]
Range <sup>‡</sup>	0.0+ to 22.8+

DOR=duration of response; CI=confidence interval; CR=complete response; PR=partial response; NR=not reached.

\* Evaluable for efficacy.

† KM method was used to obtain 2-sided 95% confidence intervals.

‡ A + sign indicates a censored value.

Response durations were longer in patients who achieved a CR, as compared to patients with a best response of PR (Table 6). Of the 104 patients who achieved CR, 68 (65%) had remission lasting at least 6 months and 64 (62%) had remission lasting at least 9 months.

Of the 287 patients who underwent leukapheresis and had radiographically evaluable disease, 27 additional patients achieved a response, apart from the responses noted in Table 5. The IRC-assessed overall response rate in the leukapheresed population (n=287) was 59% (95% CI: 53, 64), with a CR rate of 43% (95% CI: 37, 49) and PR rate of 15% (95% CI: 11, 20). These efficacy results include responses that may have been contributed solely by bridging therapy, responses after receipt of product outside of the intended dose range, and responses to product that did not meet release specifications.

## 15 REFERENCES

1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124:188-195.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

BREYANZI consists of genetically modified autologous T cells, supplied in vials as separate frozen suspensions of each CD8 component (NDC 73153-901-08) and CD4 component (NDC 73153-902-04). Each CD8 or CD4 component is packed in a carton containing up to 4 vials, depending upon the concentration of the cryopreserved drug product CAR-positive viable T cells. The cartons for each CD8 component and CD4 component are in an outer carton (NDC 73153-900-01). BREYANZI is shipped directly to the cell lab or clinical pharmacy associated with the infusion center in the vapor phase of a liquid nitrogen shipper. A Release for Infusion (RFI) Certificate for each component and patient-specific syringe labels are affixed inside the shipper.

- Confirm patient identity upon receipt.
- Store vials in the vapor phase of liquid nitrogen (less than or equal to minus 130°C) in a temperature-monitored system.
- Thaw BREYANZI prior to infusion [*see Dosage and Administration (2.2)*].

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ensure that patients understand the risk (11%) of manufacturing failure. In case of a manufacturing failure, a second manufacturing of BREYANZI may be attempted. While the patient awaits the product, additional bridging therapy (not the lymphodepletion) may be necessary. This bridging therapy may be associated with adverse events during the pre-infusion period, which could delay or prevent the administration of BREYANZI.

Prior to infusion, advise patients of the following risks:

- Cytokine Release Syndrome (CRS) – Signs and symptoms of CRS (fever, chills, hypotension, tachycardia, hypoxia, and fatigue). Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time [*see Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].
- Neurologic Toxicities – Signs or symptoms associated with neurologic events including encephalopathy, confusion, decreased consciousness, speech disorders, tremor, and seizures. Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time [*see Warnings and Precautions (5.2) and Adverse Reactions (6.1)*].
- Serious Infections – Signs or symptoms associated with infection [*see Warnings and Precautions (5.5) and Adverse Reactions (6.1)*].
- Prolonged Cytopenias – Signs or symptoms associated with bone marrow suppression including neutropenia, anemia, thrombocytopenia, or febrile neutropenia [*see Warnings and Precautions (5.6) and Adverse Reactions (6.1)*].

Advise patients of the need to:

- Contact Bristol-Myers Squibb at 1-888-805-4555 if they are diagnosed with a secondary malignancy [*see Warnings and Precautions (5.8)*].
- Refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after BREYANZI administration [*see Warnings and Precautions (5.9)*].

Manufactured by Juno Therapeutics Inc., a Bristol-Myers Squibb Company, Bothell, WA 98021.

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**MEDICATION GUIDE**  
**BREYANZI® (pronounced braye an' zee)**  
**(lisocabtagene maraleucel)**

Read this Medication Guide before you start your BREYANZI treatment. The more you know about your treatment, the more active you can be in your care. Talk with your healthcare provider if you have questions about your health condition or treatment. Reading this Medication Guide does not take the place of talking with your healthcare provider about your treatment.

**What is the most important information I should know about BREYANZI?**

BREYANZI may cause side effects that are life-threatening and can lead to death. Call your healthcare provider or get emergency help right away if you get any of the following:

- difficulty breathing
- fever (100.4°F/38°C or higher)
- chills/shaking chills
- confusion
- severe nausea, vomiting, diarrhea
- fast or irregular heartbeat
- dizziness/lightheadedness
- severe fatigue or weakness

It is important that you tell your healthcare providers that you have received BREYANZI and to show them your BREYANZI Patient Wallet Card. Your healthcare provider may give you other medicines to treat your side effects.

**What is BREYANZI?**

BREYANZI is for the treatment of large B-cell lymphoma in patients when at least 2 previous treatments have not worked or have stopped working. BREYANZI is a medicine made from your own white blood cells; the cells are genetically modified to recognize and attack your lymphoma cells.

**How will I receive BREYANZI?**

- BREYANZI is made from your own white blood cells, so your blood will be collected by a process called "leukapheresis" (LOO-kuh-feh-REE-sis).
- It takes about 3-4 weeks from the time your cells are received at the manufacturing site and are available to be shipped back to your healthcare provider, but the time may vary.
- Before you get BREYANZI, you will get 3 days of chemotherapy to prepare your body.
- When your BREYANZI is ready, your healthcare provider will give it to you through a catheter (tube) placed into your vein (intravenous infusion). BREYANZI is given as infusions of 2 different cell types.
  - You will receive infusions of one cell type, immediately followed by the other cell type.
  - The time for infusion will vary, but will usually be less than 15 minutes for each of the 2 cell types.

- During the first week, you will be monitored daily by the facility where you received your treatment.
- You should plan to stay close to this location for at least 4 weeks after getting BREYANZI. Your healthcare provider will check to see that your treatment is working and help you with any side effects that may occur.
- You may be hospitalized for side effects and your healthcare provider will discharge you if your side effects are under control, and it is safe for you to leave the hospital.
- Your healthcare provider will want to do blood tests to follow your progress. It is important that you do have your blood tested. If you miss an appointment, call your healthcare provider as soon as possible to reschedule.

### **What should I avoid after receiving BREYANZI?**

- Do not drive, operate heavy machinery, or do other activities that could be dangerous if you are not mentally alert, for at least 8 weeks after you get BREYANZI. This is because the treatment can cause temporary memory and coordination problems, including sleepiness, confusion, dizziness, and seizures.
- Do not donate blood, organs, tissues, or cells for transplantation.

### **What are the possible or reasonably likely side effects of BREYANZI?**

The most common side effects of BREYANZI are:

- fatigue
- difficulty breathing
- fever (100.4°F/38°C or higher)
- chills/shaking chills
- confusion
- difficulty speaking or slurred speech
- severe nausea, vomiting, diarrhea
- headache
- dizziness/lightheadedness
- fast or irregular heartbeat
- swelling

BREYANZI can increase the risk of life-threatening infections that may lead to death. Tell your healthcare provider right away if you develop fever, chills, or any signs or symptoms of an infection.

BREYANZI can lower one or more types of your blood cells (red blood cells, white blood cells, or platelets). After treatment, your healthcare provider will test your blood to check for this. Tell your healthcare provider right away if you get a fever, are feeling tired, or have bruising or bleeding.

Having BREYANZI in your blood may cause a false-positive HIV test result by some commercial tests.

These are not all the possible side effects of BREYANZI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **General information about the safe and effective use of BREYANZI**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about BREYANZI, talk with your healthcare provider. You can ask your healthcare provider for information about BREYANZI that is written for health professionals.

For more information, go to [BREYANZI.com](http://BREYANZI.com) or call 1-888-805-4555.

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Pat. <https://www.bms.com/patient-and-caregivers/our-medicines.html>  
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This Medication Guide has been approved by the U.S. Food and Drug Administration.  
Issued: FEB 2021

## **PRINCIPAL DISPLAY PANEL - Kit Carton**

lisocabtagene maraleucel  
Breyanzi™

lisocabtagene maraleucel  
Breyanzi®

NDC 73153-900-01  
Rx only

FOR AUTOLOGOUS & INTRAVENOUS USE ONLY

Dispense with Medication Guide

Dosage: 50 to 110 x 10<sup>6</sup> CAR-positive viable T cells.  
See Release for Infusion Certificate (inside shipper).

Contains DMSO 7.5% v/v.

1 to 4 single-dose vials/component. Each vial  
contains 1.5 to 70 x 10<sup>6</sup> CAR-positive viable T cells/mL.  
4.6 mL per vial.

Store at ≤ -130°C; vapor phase of liquid nitrogen.  
Do not filter or irradiate.  
Not evaluated for infectious substances.  
Discard unused portion.

Manufactured by:  
Juno Therapeutics, Inc., a Bristol-Myers Squibb Company  
Bothell, WA 98021  
Phone: 1-888-805-4555  
US License #: 2156

111633

VERIFY  
PATIENT  
ID

First: FIRST NAME  
Last: LAST NAME  
Date of birth: DD-MMM-YYYY  
JOIN: XXXX-XXXXX  
Aph ID/DIN: XXX XXX XXX XXX

CD8  
component

CD4  
component

Lot  
XXXX-XXXXXY  
XXXX-XXXXXY

Expiration  
DD-MMM-YYYY  
DD-MMM-YYYY

STOP  
Confirm patient ID  
prior to infusion

# lisocabtagene maraleucel

**Breyanzi**<sup>™</sup>

lisocabtagene maraleucel NDC 73153-900-01  
Breyanzi<sup>®</sup> Rx only

**FOR AUTOLOGOUS & INTRAVENOUS USE ONLY**

**Dispense with Medication Guide**

**Dosage:** 50 to 110 x 10<sup>6</sup> CAR-positive viable T cells.  
See Release for Infusion Certificate (inside shipper).

Contains DMSO 7.5% v/v.

**1 to 4 single-dose vials/component. Each vial contains 1.5 to 70 x 10<sup>6</sup> CAR-positive viable T cells/mL. 4.6 mL per vial.**

**Store at ≤ -130°C; vapor phase of liquid nitrogen.**

**Do not filter or irradiate.**

Not evaluated for infectious substances.

**Discard unused portion.**

**Manufactured by:**

**Juno Therapeutics, Inc., a Bristol-Myers Squibb Company**

Bothell, WA 98021

Phone: 1-888-805-4555 US License #: 2156



111633



NDC 73153-900-01

**VERIFY  
PATIENT  
ID**

First: **FIRST NAME**

Last: **LAST NAME**

Date of birth: **DD-MMM-YYYY**

JOIN: **XXXX-XXXXX**

Aph ID/DIN: **XXX XXX XXX XXX**



**CD8  
component**

**CD4  
component**

**Lot** XXXX-XXXXXY

XXXX-XXXXXY

**Expiration** DD-MMM-YYYY

DD-MMM-YYYY



**Confirm patient ID  
prior to infusion**

## BREYANZI

lisocabtagene maraleucel kit

### Product Information

<b>Product Type</b>	CELLULAR THERAPY	<b>Item Code (Source)</b>	NDC:73153-900
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### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:73153-900-01	1 in 1 CARTON		

## Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, SINGLE-DOSE	5 mL
Part 2	1 VIAL, SINGLE-DOSE	5 mL

## Part 1 of 2

### BREYANZI (CD4)

lisocabtagene maraleucel injection, suspension

## Product Information

Item Code (Source)	NDC:73153-902
Route of Administration	INTRAVENOUS

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LISOCABTAGENE MARALEUCEL (UNII: 7K2YOJ14X0) (LISOCABTAGENE MARALEUCEL - UNII: 7K2YOJ14X0)	LISOCABTAGENE MARALEUCEL	50000000 in 5 mL

## Inactive Ingredients

Ingredient Name	Strength
DIMETHYL SULFOXIDE (UNII: YOW8V9698H)	
ALBUMIN HUMAN (UNII: ZIF514RVZR)	

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:73153-902-04	5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125714	02/05/2021	

## Part 2 of 2

### BREYANZI (CD8)



lisocabtagene maraleucel injection, suspension

### Product Information

**Item Code (Source)** NDC:73153-901

**Route of Administration** INTRAVENOUS

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>LISOCABTAGENE MARALEUCEL</b> (UNII: 7K2YOJ14X0) (LISOCABTAGENE MARALEUCEL - UNII:7K2YOJ14X0)	LISOCABTAGENE MARALEUCEL	50000000 in 5 mL

### Inactive Ingredients

Ingredient Name	Strength
<b>DIMETHYL SULFOXIDE</b> (UNII: YOW8V9698H)	
<b>ALBUMIN HUMAN</b> (UNII: ZIF514RVZR)	

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:73153-901-08	5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125714	02/05/2021	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125714	02/05/2021	

**Labeler** - Juno Therapeutics, Inc. (079290042)